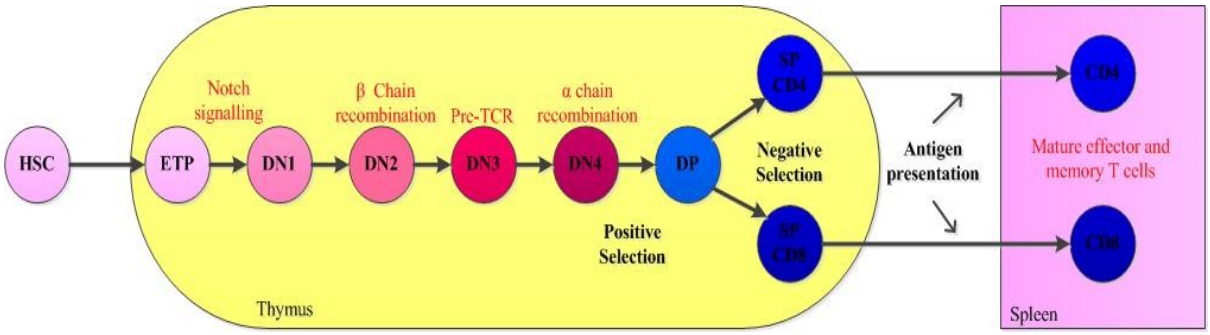
Part II Pathology lectures: Dr Donald Palmer Thymus Biology and Central Tolerance

The thymus is the unique site of T cell development. Stem cells from the bone marrow migrate to the thymus where they receive the appropriate signals to become immune competent T cells. These signals are from the thymic microenvironment, includes both cell-cell and soluble factors. During development, T cells are required to pass several checkpoints and under several rounds of selection to become restricted and self-tolerant CD4+ and CD8+ T cells. The thymus is responsible for the formation of self-restricted, immunocompetent T cells. A schematic diagram of T cell development is below.



MHC class I and MHC class II are required for positive selection of $CD8^+$ and $CD4^+$ single positive (SP) thymocytes respectively. Positive selection occurs when thymocytes expressing a functional TCR are able to recognise self-MHC and peptide with an appropriate affinity (Naeher *et al.*, 2007). Thymocytes that bind with a high affinity are killed by apoptosis, protecting from autoreactive T cells, and those that bind with a low affinity die by neglect. After successful positive selection the cells become SP ($CD4^+CD8^-$ or $CD8^+CD4^-$) and migrate to the medullary region via a chemokine gradient. Once in the medullary region, these cells undergo a process called negative selection which forms part of central tolerance, preventing the circulation of autoreactive T cells in the periphery. Negative selection occurs primarily by mTEC which are able to express peripheral, tissue-specific antigens. This phenomenon occurs via the expression of autoimmune regulator (AIRE) gene by mTEC, which acts as a novel transcription regulator allowing the production of gene products that are tissue-specific antigens.

At the end of these two lectures, students should be able to:

1. Describe how T cells recognise antigen.
2. Describe the basic structure of the T cell receptor and how T cell receptor diversity is achieved.
3. Describe function of the thymus.
4. Describe the developmental pathway of T cells.
5. Describe the role of the microenvironment in T cell differentiation.
6. Describe how tolerance is generated.

References:

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